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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/525,992	ARORA ET AL.	
	Examiner	Art Unit	
	Amy L. Clark	1655	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 June 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above claim(s) *7-9 and 12-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6 and 21-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Acknowledgment is made of the receipt and entry of the amendment filed on 06/11/2008 with the amendment of claim 1, 2 and 23-25, and newly added claim 26.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Election/Restrictions

Claims 1-26 are currently pending.

This application contains claims 7-9 and 12-20 drawn to an invention nonelected with traverse in the reply filed on 30 May 2006. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claims 7-9 and 12-20 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 30 May 2006.

Claims 1-6, 10, 11 and 21-26 are under examination.

Claim Rejections - 35 USC § 112

Claims 1-6, 10, 11 and 21-26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to

reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Newly applied as necessitated by amendment.

In the amended claim 1 and claim 2, Applicant claims, "an aqueous, alcoholic, or hydroalcoholic extract of a pericarp of the fruit of *Sapindus trifoliatus*, comprising of total saponins expressed as hederagenin from 0.001 to 1.0% (w/v) and at least one pharmaceutically acceptable additive", thereby introducing "comprising of total saponins expressed as hederagenin from 0.001 to 1.0% (w/v)", which is considered to be new matter. Insertion of the above mentioned claim limitation has no support in the as-filed specification. The insertion of the limitation is a new concept because it neither has literal support in the as-filed specification by way of generic disclosure, nor are there specific examples of the newly limited genus which would show possession of the concept for "comprising of total saponins expressed as hederagenin from 0.001 to 1.0% (w/v)". The originally filed specification discloses: "the present inventors have found that the aqueous, alcoholic or hydroalcoholic extract containing a mixture of triterpenoid saponins derived from S. trifoliatus are estimated to contain 4-8 (% w/w) of hederagenin. The extract does not cause damage or irritation to the nasal mucous membrane, when administrated intranasally, thereby providing a safe, simple, convenient and cost-effective method for treatment of migraine...aqueous, alcoholic or hydroalcoholic extract containing a mixture of triterpenoid saponins derived from S. trifoliatus are estimated to contain 4-8 (% w/w) of hederagenin...the present invention provides a pharmaceutical composition containing an extract comprising a mixture of

triterpenoid saponins derived from S. trifoliatus, which further comprises 0.001 to 1.0 (% w/v), of hederagenin, which exhibits excellent anticonvulsant activity, which in turn when administrated intranasally is suitable for the prophylactic treatment of migraine (See paragraphs 0066 and 0067)...

The saponins present in the aqueous/alcoholic or aqueous-alcoholic extract [2] have been isolated and identified. The aqueous/alcoholic, aqueous-alcoholic extract of S. trifoliatus [2] was fractionated with n-butanol. The butanol layer was concentrated to give a solid. This was dissolved in methanol and adsorbed on silica gel. The column was eluted with chloroform-methanol with increasing proportions of methanol (2, 4, 6 etc.). Fractions were collected to yield six crude compounds. Further purification was done by repeated flash chromatography on silica gel to yield compounds 5-10, again using chloroform-methanol with increasing proportions of methanol (2, 4, 6 etc.). Each of these 6 hedragenins derivatives were characterized and identified by spectral methods.

Compound [5] Hederagenin-3-O-(.alpha.-L-arabinopyranosyl-(1 - - - 3)-.alpha.-L-rhamnopyranosyl-(1 - - - 2)-.beta.-D-xylopyranoside

Compound [6] Hederagenin-3-O-(3-O-acetyl-.beta.-D-xylopyranosyl-(1 - - - 3)-.alpha.-L-rhamnopyranosyl-(1 - - - 2)-.alpha.-L-arabinopyranosid- e

Compound [7] Hederagenin-3-O-(4-O-acetyl-.beta.-D-xylopyranosyl-(1 - - - 3)-.alpha.-L-rhamnopyranosyl-(1 - - - 2)-.alpha.-L-arabinopyranosid- e

Compound [8] Hederagenin-3-O-(3,4-O-diacetyl-.beta.-D-xylopyranosyl- -(1 - - - 3)-.alpha.-L-rhamnopyranosyl -(1 - - - 2)-.alpha.-L-arabinopyran- oside

Compound [9] Hederagenin-3-O-(.beta.-D-xylopyranosyl-(1 - - - 3)-.alpha.-L-rhamnopyranosyl-(1 - - - 2)-.beta.-D-xylopyranoside

Compound [10] Hederagenin-3-O-(.beta.-D-xylopyranosyl-(1 - - - 3)-.alpha.-L-rhamnopyranosyl-(1 - - - 2)-.beta.-D-xylopyranoside

Acid hydrolysis of the extract yielded only one aglycone, which was identified as hederagenin. Therefore, estimation of the abovementioned saponins present in the aqueous/alcoholic or aqueous/alcoholic extract [2] was calculated as hederagenin. The content of hederagenin was estimated in the extract by boiling it with 50% methanolic HCl. The entire mixture was evaporated to dryness. This was reconstituted in methanol and estimated by HPLC. The concentration of hederagenin was found to be between 4-8% w/w of the extract (See paragraphs 0103-0110)."

This is not sufficient support for the new limitation: "comprising of total saponins expressed as hederagenin from 0.001 to 1.0% (w/v)". This is a matter of written description, not a question of what one of skill in the art would or would not have known.

The material within the four corners of the as-filed specification must lead to the generic concept. If it does not, the material is new matter. Declarations and new references cannot demonstrate the possession of a concept after the fact. Thus, the insertion of the above mentioned claim-limitation is considered to be the insertion of new matter for the above reasons.

As the above- mentioned claim limitation could not be found in the present specification, the recitation of the claim limitation is deemed new matter; and, therefore

it must be omitted from the claim language, unless Applicant can particularly point to the specification for literal support.

Claims 1-6, 10, 11 and 21-26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Newly applied as necessitated by amendment.

The metes and bounds of claim 1 and claim 2 are rendered uncertain by the phrase "an aqueous, alcoholic, or hydroalcoholic extract of a pericarp of the fruit of *Sapindus trifoliatus*, comprising of total saponins expressed as hederagenin from 0.001 to 1.0% (w/v)" because it is unclear as to whether Applicant means that the all of the saponins are hederagenin or if the extract itself is expressed as hederagenin and comprises total saponins. The lack of clarity renders the claims indefinite since the resulting claims do not clearly set forth the metes and bounds of the patent protection desired.

Response to Arguments

Claim Objections

Claims 21-25 remain objected to and newly added claim 26 is objected to because of the following informalities: Claims 21-26 are redundant and appear to recite the same limitation as claim 1 and should, therefore, either be cancelled or amended. Appropriate correction is required.

This rejection is maintained for reasons of record set forth in the paper mailed on 12/13/2007.

Claim Rejections - 35 USC § 112

Claim 1-6, 10, 11 and 21-25 remain rejected and newly added claim 26 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

This rejection is maintained for reasons of record set forth in the paper mailed on 12/13/2007.

Claim 1 still recites the limitation "the fruit" in line 8. There is insufficient antecedent basis for this limitation in the claim.

Claims 1-6, 10, 11 and 21-25 remain rejected and newly added claim 26 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a pharmaceutical composition for the prophylactic treatment of migranes comprising an aqueous extract of *Sapindus trifoliatus* pericap (0.1-1 % w/v) and *Emblica officinalis* (0.1-1 % w/v), does not reasonably provide enablement for an anticonvulsant pharmaceutical composition for nasal administration having a binding affinity for at least one receptor site selected from the group consisting of Gamma-Amino Butyric Acid (GABA)-A agonist site, Glutamate- alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) site, Glutamate-Kainate site, Glutamate: N-methyl-D-

aspartic acid (NMDA) agonistic site, Glutamate- N-methyl-D-aspartic acid (NMDA) glycine (strychnine insensitive) site and Sodium channel (site 2), consisting essentially of: i. an aqueous, alcoholic, or hydroalcoholic extract of the pericarp of the fruit of *Sapindus trifoliatus*, comprising an aqueous, alcoholic, or hydroalcoholic extract of a pericarp of the fruit of *Sapindus trifoliatus*, comprising of total saponins expressed as hederagenin from 0.001 to 1.0% (w/v), and ii. at least one pharmaceutically acceptable additive, nor does it reasonably provide enablement for an anticonvulsant pharmaceutical composition, for nasal administration according to claim 1, being suitable for prophylactic treatment of migrane mediated through its anticonvulsant activity. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

This rejection is maintained for reasons of record set forth in the paper mailed on 12/13/2007 and repeated below, slightly altered to take into consideration Applicant's amendment filed on 06/11/2008.

Applicant's arguments have been thoroughly considered, but the rejection remains the same for the reasons set forth in the previous Office action and for the reasons set forth below.

Enablement is considered in view of the *Wands* factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art predictability of the art and the amount of experimentation necessary. All of the Wands factors have been

considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the Invention: The nature of this invention is complex in that it is drawn to an anticonvulsant pharmaceutical composition for nasal administration having a binding affinity for at least one receptor site selected from the group consisting of Gamma-Amino Butyric Acid (GABA)-A agonist site, Glutamate- alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) site, Glutamate-Kainate site, Glutamate: N-methyl-D-aspartic acid (NMDA) agonistic site, Glutamate- N-methyl-D-aspartic acid (NMDA) glycine (strychnine insensitive) site and Sodium channel (site 2), consisting essentially of: i. an aqueous, alcoholic, or hydroalcoholic extract of the pericarp of the fruit of *Sapindus trifoliatus,* comprising from 0.001 to 1.0 (% w/v) of hederagenin, and ii. at least one pharmaceutically acceptable additive, it is also drawn to an anticonvulsant pharmaceutical composition, for nasal administration according to claim 1, being suitable for prophylactic treatment of migraine, mediated through its anticonvulsant activity.

While a pharmaceutical composition for the prophylactic treatment of migranes comprising aqueous extracts of *Sapindus trifoliatus* pericap was known, it was not known or demonstrated in the art or in the specification that to a pharmaceutical composition for nasal administration consisting essentially of: i. an aqueous, alcoholic, or hydroalcoholic extract of the pericarp of the fruit of *Sapindus trifoliatus,* comprising from 0.001 to 1.0 (% w/v) of hederagenin, and ii. at least one pharmaceutically acceptable additive is capable of having a binding affinity for at least one receptor site

selected from the group consisting of Gamma-Amino Butyric Acid (GABA)-A agonist site, Glutamate- alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) site, Glutamate-Kainate site, Glutamate: N-methyl-D-aspartic acid (NMDA) agonistic site, Glutamate- N-methyl-D-aspartic acid (NMDA) glycine (strychnine insensitive) site and Sodium channel (site 2), is suitable for prophylactic treatment of migraine, mediated through its anticonvulsant activity or is capable of the other functions claimed by Applicant. Furthermore, it was not known or demonstrated in the art or in the specification how a composition comprising an aqueous extract of *Sapindus trifoliatus* pericap is capable of prophylactic treatment of migranes (please note that there is no mechanism of action that demonstrates that the claimed composition has any of these claimed effects). Please note that Applicant is also claiming this activity for alcoholic and hydroalcoholic extracts of pericarp of the fruit of *Sapindus trifoliatus*, however, there are no working examples at all with regards to these extracts.

Breadth of the Claims: The claims are broad in that a composition comprising: transfer factor; and at least one support component in an amount that prevents, mitigates, or reverses at least one aspect of dysfunction of the metabolism or endocrine system function of the subject, wherein the transfer factor is a mammalian transfer factor; and the at least one support component is bitter melon and Indian kino; the composition of claim 1, wherein the at least one support component facilitates insulin production by β cells of the pancreas of the subject, improves insulin sensitivity, regulates production of glucose or prevents glucose from exiting cells in claim 6; and the composition of claim 1, consisting essentially of the transfer factor and the at least

one support component in claim 10, wherein each of the compositions may be administered to support or regulate the metabolism of a subject. The complex nature of the subject matter of this invention is greatly exacerbated by the breadth of the claims.

Guidance of the Specification and Existence of Working Examples: The specification describes an aqueous extract of *Sapindus trifoliatus* displays binding affinity for $GABA_A$ agonistic site in bovine cerebellum, and in Glutamate AMPA site in rat forebrain, Glutamate Kainate site in rat forebrain, Glutamate NMDA agonist site in rat forebrain, Glutamate NMDA Glycine (strychenine-insensitive site) in rat cortex and hippocampus, GABA chloride TBOB in rat cortex, Glutamate chloride in rat cerebellum, and Sodium site 2 in rat forebrain when in higher concentrations (See page 19, Table 1). Please note that there is no description of how these studies were conducted or how the results were obtained. All that has been provided was a table with results. The specification further discloses that in an *in vivo* rat study, an aqueous extract of *Sapindus trifoliatus* was administered intranasally to rats and thirty minutes after administration, rats were administered electroshock. The specification further discloses that an aqueous extract of *Sapindus trifoliatus* does not protect against PTZ induced convulsions in rats on intra-nasal administration (See pages 20-23). The specification further discloses a method of evaluation of motor co-ordination on rota rod performance test in rats with an aqueous extract of *Sapindus trifoliatus* (See pages 23-26).

The specification envisions that a pharmaceutical composition for nasal administration consisting essentially of: i. an aqueous, alcoholic, or hydroalcoholic extract of the pericarp of the fruit of *Sapindus trifoliatus,* comprising from 0.001 to 1.0 (%

w/v) of hederagenin, and ii. at least one pharmaceutically acceptable additive will have utility in humans as an anticonvulsant by having a binding affinity for at least one receptor site selected from the group consisting of Gamma-Amino Butyric Acid (GABA)-A agonist site, Glutamate- alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) site, Glutamate-Kainate site, Glutamate: N-methyl-D-aspartic acid (NMDA) agonistic site, Glutamate- N-methyl-D-aspartic acid (NMDA) glycine (strychnine insensitive) site and Sodium channel (site 2) and will also provide prophylactic treatment of migraine mediated through its anticonvulsant activity.

However, no working examples are provided with regard to a pharmaceutical composition for nasal administration consisting essentially of: i. an aqueous, alcoholic, or hydroalcoholic extract of the pericarp of the fruit of *Sapindus trifoliatus,* comprising from 0.001 to 1.0 (% w/v) of hederagenin, and ii. at least one pharmaceutically acceptable additive wherein each of the compositions acts as an anticonvulsant by having a binding affinity for at least one receptor site selected from the group consisting of Gamma-Amino Butyric Acid (GABA)-A agonist site, Glutamate- alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) site, Glutamate-Kainate site, Glutamate: N-methyl-D-aspartic acid (NMDA) agonistic site, Glutamate- N-methyl-D-aspartic acid (NMDA) glycine (strychnine insensitive) site and Sodium channel (site 2) or that each of the compositions provides prophylactic treatment of migraine mediated through its anticonvulsant activity. Furthermore, no working examples are provided that demonstrate the efficacy of a pharmaceutical composition for nasal administration consisting essentially of: i. an aqueous, alcoholic, or hydroalcoholic extract of the

pericarp of the fruit of *Sapindus trifoliatus,* comprising from 0.001 to 1.0 (% w/v) of hederagenin, and ii. at least one pharmaceutically acceptable additive wherein each of the compositions acts as an anticonvulsant by having a binding affinity for at least one receptor site selected from the group consisting of Gamma-Amino Butyric Acid (GABA)-A agonist site, Glutamate- alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) site, Glutamate-Kainate site, Glutamate: N-methyl-D-aspartic acid (NMDA) agonistic site, Glutamate- N-methyl-D-aspartic acid (NMDA) glycine (strychnine insensitive) site and Sodium channel (site 2) or that each of the compositions provides prophylactic treatment of migraine mediated through its anticonvulsant activity.

Predictability and State of the Art: The state of the art at the time the invention was made was unpredictable and underdeveloped. For example, Katsumori et al. (U, "Acute Effects of Various GABA Receptor Agonists and Glutamate Antagonists on Focal Hippocampal Seizures in Freely Moving Rats Elicited by Low-Frequency Stimulation" Synapse, Vol. 28 (1998) 103-109) teaches that although there is a large volume of scientific data indicating that the pathogenesis of epileptic seizures may result from (1) an attenuation in the function/activity of GABAergic neurons, and/or (2) an overactivity of neurons that use excitatory amino acides, such as 1-glutamate, pharmacological agents that act as $GABA_A$ receptor antagonists or as agonists at certain excitatory amino acid receptors will precipitate seizures (See page 103). Katsumori further teaches that by contrast, the systemic administration of antagonists of the excitatory amino receptor subtypes n-methyl-d-aspartate (NMDA) and kainic acid have been shown to be effective in blocking epileptic seizures generated in animals, although a

number of these agents produce significant adverse behavioral alterations, such as ataxia and sedation (See page 104). Katsumori further teaches that $GABA_A$ receptors may play a role in maintenance, but not in the initiation of seizures, whereas, in contrast, seizure initiation may be predominately mediated by glutamate receptors, whereas AMPA receptors may be involved in mediating the initiation and maintenance of seizures (See page 108). Therefore, it is unclear exactly what mechanism is responsible for epileptic seizures and which binding sites are responsible for which aspect of a seizure. Finally, Misikostas et al. (V, "Receptor Systems Mediating *c-fos* Expression within Trigeminal Nucleus Caudalis in Animal Models of Migraine" Brain Res Rev Vol 35 (2001) 20-35) teaches that although there is evidence at least ten receptors including $GABA_A$, NMDA and AMPA modulate *c-fos* expression within Sp5C, to date there is no adequate model of migrane. Misikostas further teaches that although the use of *c-fos* as a marker of activation of the trigeminovascular system as it relates to cephalic pain has produced notable advances in the field of pharmacology and pathophysiology of migrane, not all drugs that modulate *c-fos* expression within Sp5C have clinical significance (See page 29, "Conclusions") and that there are limitations on the *c-fos* paradigm of migrane, that the affinity profile to specific receptor subtypes of tested drugs, as well as their pharmacokinetic and pharmacodynamic profile, vary from the animals to man. Misikostas further teaches that not all receptors that modulate *c-fos* expression within Sp5C have equal clinical importance and that the experimental techniques used for *c-fos* induction in animals do not reproduce the generator of a migrane attack, which remains unknown. Misikostas further teaches that expression

within other nuclei further limits the value of the rodent/feline model (See page 30). Therefore, it appears that it is not clear as to which receptor(s) are responsible for migrane attacks or that these receptors are have any bearing on migrane attacks and that just because a compound binds to a certain receptor, does not mean that the compound will have an effect on migranes. Furthermore, it appears that animal models are poor predictors of the effect of anti-migrane medication on humans.

As mentioned above, the only working examples provided by Applicant are drawn to an aqueous extract of *Sapindus trifoliatus*, wherein the aqueous extract of *Sapindus trifoliatus* displays binding affinity for $GABA_A$ agonistic site in bovine cerebellum, and in Glutamate AMPA site in rat forebrain, Glutamate Kainate site in rat forebrain, Glutamate NMDA agonist site in rat forebrain, Glutamate NMDA Glycine (strychenine-insensitive site) in rat cortex and hippocampus, GABA chloride TBOB in rat cortex, Glutamate chloride in rat cerebellum, and Sodium site 2 in rat forebrain. However, there is no description of how these studies were conducted or how the results were obtained. All that has been provided was a table with results. The specification further discloses that in an *in vivo* rat study, an aqueous extract of *Sapindus trifoliatus* was administered intranasally to rats and thirty minutes after administration, rats were administered electroshock. The specification further discloses that an aqueous extract of *Sapindus trifoliatus* does not protect against PTZ induced convulsions in rats on intra-nasal administration (See pages 20-23). The specification further discloses a method of evaluation of motor co-ordination on rota rod performance test in rats with an aqueous extract of *Sapindus trifoliatus*. The specification does not

show that the composition acts as an anticonvulsant by having a binding affinity for at least one receptor site selected from the group consisting of Gamma-Amino Butyric Acid (GABA)-A agonist site, Glutamate- alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) site, Glutamate-Kainate site, Glutamate: N-methyl-D-aspartic acid (NMDA) agonistic site, Glutamate- N-methyl-D-aspartic acid (NMDA) glycine (strychnine insensitive) site and Sodium channel (site 2) or that each of the compositions provides prophylactic treatment of migraine mediated through its anticonvulsant activity.

Thus, while the claim-designated compositions may be useful for providing such an effect, Applicant does not disclose a pharmaceutical composition for nasal administration consisting essentially of: i. an aqueous, alcoholic, or hydroalcoholic extract of the pericarp of the fruit of *Sapindus trifoliatus*, comprising from 0.001 to 1.0 (% w/v) of hederagenin, and ii. at least one pharmaceutically acceptable additive, wherein each of the compositions acts as an anticonvulsant by having a binding affinity for at least one receptor site selected from the group consisting of Gamma-Amino Butyric Acid (GABA)-A agonist site, Glutamate- alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) site, Glutamate-Kainate site, Glutamate: N-methyl-D-aspartic acid (NMDA) agonistic site, Glutamate- N-methyl-D-aspartic acid (NMDA) glycine (strychnine insensitive) site and Sodium channel (site 2) or that each of the compositions provides prophylactic treatment of migraine mediated through its anticonvulsant activity.

The Office further notes that while the specification discloses that the claim-

designated compositions will have utility in humans, wherein each of the compositions acts as an anticonvulsant by having a binding affinity for at least one receptor site selected from the group consisting of Gamma-Amino Butyric Acid (GABA)-A agonist site, Glutamate- alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) site, Glutamate-Kainate site, Glutamate: N-methyl-D-aspartic acid (NMDA) agonistic site, Glutamate- N-methyl-D-aspartic acid (NMDA) glycine (strychnine insensitive) site and Sodium channel (site 2) or that each of the compositions provides prophylactic treatment of migraine mediated through its anticonvulsant activity, nowhere in the specification or in the limitations does Applicant direct the claimed subject matter to the administration of a pharmaceutical composition for nasal administration consisting essentially of: i. an alcoholic, or hydroalcoholic extract of the pericarp of the fruit of *Sapindus trifoliatus,* comprising from 0.001 to 1.0 (% w/v) of hederagenin, and ii. at least one pharmaceutically acceptable additive to any subject.

Amount of Experimentation Necessary: The quantity of experimentation necessary to carry out the claimed invention is high, as the skilled artisan could not rely on the prior art or instant specification to teach how to make and use a pharmaceutical composition for nasal administration consisting essentially of: i. an aqueous, alcoholic, or hydroalcoholic extract of the pericarp of the fruit of *Sapindus trifoliatus,* comprising from 0.001 to 1.0 (% w/v) of hederagenin, and ii. at least one pharmaceutically acceptable additive, wherein each of the compositions acts as an anticonvulsant by having a binding affinity for at least one receptor site selected from the group consisting of Gamma-Amino Butyric Acid (GABA)-A agonist site, Glutamate- alpha-amino-3-

hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) site, Glutamate-Kainate site, Glutamate: N-methyl-D-aspartic acid (NMDA) agonistic site, Glutamate- N-methyl-D-aspartic acid (NMDA) glycine (strychnine insensitive) site and Sodium channel (site 2) or that each of the compositions provides prophylactic treatment of migraine mediated through its anticonvulsant activity that can be administered in a therapeutically effective dose with an acceptable level of side-effects.

In view of the breadth of the claims and the lack of guidance provided by the specification as well as the unpredictability of the art, the skilled artisan would have required an undue amount of experimentation to make and/or use the claimed invention. Therefore, claims 1-6, 10, 11 and 21-26 are not considered to be fully enabled by the instant specification.

Applicant's arguments have been fully considered but they are not persuasive.

Applicant argues that the claims are not broad nor is the subject matter complex.

In response to Applicant's argument, the claims are broad and complex in that the composition, as claimed, would be expected to have a binding affinity for at least one receptor site selected from the group consisting of Gamma-Amino Butyric Acid (GABA)-A agonist site, Glutamate- alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) site, Glutamate-Kainate site, Glutamate: N-methyl-D-aspartic acid (NMDA) agonistic site, Glutamate- N-methyl-D-aspartic acid (NMDA) glycine (strychnine insensitive) site and Sodium channel (site 2). The art does not teach or fairly suggest this, as set forth above and as set forth in the previous Office Action.

Applicant argues that the nature of the invention is the level of one of ordinary

skill in the art and having benefit of the application as originally filed and the Chikara reference, one of ordinary skill in the art would have been able to practice the claimed invention without undue experimentation and all that one of ordinary skill in the art would need to do is substitute the claimed invention for what is taught in Chikara.

In response to Applicant's argument, the Examiner has established a reasonable basis to question the enablement provided for the claimed invention. The *Wands* factors constitute a basic test of enablement. The claimed invention is drawn to an anticonvulsant pharmaceutical composition for nasal administration having a binding affinity for at least one receptor site selected from the group consisting of Gamma-Amino Butyric Acid (GABA)-A agonist site, Glutamate- alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) site, Glutamate-Kainate site, Glutamate: N-methyl-D-aspartic acid (NMDA) agonistic site, Glutamate- N-methyl-D-aspartic acid (NMDA) glycine (strychnine insensitive) site and Sodium channel (site 2), consisting essentially of: i. an aqueous, alcoholic, or hydroalcoholic extract of the pericarp of the fruit of *Sapindus trifoliatus,* comprising an aqueous, alcoholic, or hydroalcoholic extract of a pericarp of the fruit of *Sapindus trifoliatus*, comprising of total saponins expressed as hederagenin from 0.001 to 1.0% (w/v), and ii. at least one pharmaceutically acceptable additive. Applicant asserts that Applicant's composition has a binding affinity for at least one receptor site selected from the group consisting of Gamma-Amino Butyric Acid (GABA)-A agonist site, Glutamate- alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) site, Glutamate-Kainate site, Glutamate: N-methyl-D-aspartic acid (NMDA) agonistic site, Glutamate- N-methyl-D-aspartic acid (NMDA)

glycine (strychnine insensitive) site and Sodium channel (site 2); however, it is not known in the art how to use the composition commensurate in scope to how Applicant proposes the composition is to be used. For example, the ingredients claimed by Applicant have not been found in the art to have the claimed functional effect claimed by Applicant and since the results provided by Applicant in Applicant's specification are inconclusive for the reasons set forth above and in the previous Office Action, it can be concluded that using Applicant's claimed invention in the manner instantly claimed would require undue experimentation, as set forth above and in the previous Office Action through the *Wands* analysis.

In further response to Applicant's arguments, although Applicant discloses a method of obtaining an aqueous extract of the pericarp of the fruit of *Sapindus trifoliatus*, Applicant has failed to show that an aqueous extract of the pericarp of the fruit of *Sapindus trifoliatus* is having a binding affinity for at least one receptor site selected from the group consisting of Gamma-Amino Butyric Acid (GABA)-A agonist site, Glutamate- alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) site, Glutamate-Kainate site, Glutamate: N-methyl-D-aspartic acid (NMDA) agonistic site, Glutamate- N-methyl-D-aspartic acid (NMDA) glycine (strychnine insensitive) site and Sodium channel (site 2), since the binding of these sites is unpredictable, as mentioned above. Therefore, Applicant is not fully enabled, particularly in view of the unpredictability of the art at the time the invention was made, as shown above.

In response to Applicant's argument that it is not necessary to provide working examples for each and every mode of making and using the invention, Applicant is

directed to MPEP 2164.03, wherein the MPEP states:

The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. **In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling.** See, e.g., *Chiron Corp. v. Genentech Inc.*, 363 F.3d 1247, 1254, 70 USPQ2d 1321, 1326 (Fed. Cir. 2004),

The "predictability or lack thereof" in the art refers to the ability of one skilled in the art to extrapolate the disclosed or known results to the claimed invention. On the other hand, **if one skilled in the art cannot readily anticipate the effect of a change within the subject matter to which that claimed invention pertains, then there is lack of predictability in the art**. Accordingly, what is known in the art provides evidence as to the question of predictability. *In re Marzocchi*, 439 F.2d 220, 223-24, 169 USPQ 367, 369-70 (CCPA 1971). *In re Vickers*, 141 F.2d 522, 526-27, 61 USPQ 122, 127 (CCPA 1944); *In re Cook*, 439 F.2d 730, 734, 169 USPQ 298, 301 (CCPA 1971); *In re Soll*, 97 F.2d 623, 624, 38 USPQ 189, 191 (CCPA 1938); *In re Fisher*, 427 F.2d 833,

839, 166 USPQ 18, 24 (CCPA 1970) . See also *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *In re Vaeck*, 947 F.2d 488, 496, 20 USPQ2d 1438, 1445 (Fed. Cir. 1991).

The Examiner's basis of the 112 1st rejection under *In re Wands* describes what Applicant has disclosed in Applicant's specification, which is fact, and the Examiner is further stating that no working examples, either in the art or in Applicant's own specification, exists to show the efficacy of an aqueous, alcoholic, or hydroalcoholic extract of a pericarp of the fruit of *Sapindus trifoliatus*, comprising of total saponins expressed as hederagenin from 0.001 to 1.0% (w/v) having a binding affinity for at least one receptor site selected from the group consisting of Gamma-Amino Butyric Acid (GABA)-A agonist site, Glutamate- alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) site, Glutamate-Kainate site, Glutamate: N-methyl-D-aspartic acid (NMDA) agonistic site, Glutamate- N-methyl-D-aspartic acid (NMDA) glycine (strychnine insensitive) site and Sodium channel (site 2). Therefore, it is a question of what one of ordinary skill in the art knew at the time the invention was made and whether one or ordinary skill in the art would know how to use the invention commensurate in scope with Applicant's claims, which the Examiner has demonstrated one of ordinary skill in the art is incapable of doing.

Please note that the art rejections below are based upon what Applicant is enabled for based upon Applicant's originally filed specification and what was known in the art at the time the invention was made.

Claim Rejections - 35 USC § 103

Claims 1-6, 10 and 11 remain rejected and claims 21-26 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over Chikara et al. (N*).

This rejection is maintained for reasons of record set forth in the paper mailed on 12/13/2007 and repeated below, slightly altered to take into consideration Applicant's amendment filed on 06/11/2008.

Applicant's arguments have been thoroughly considered, but the rejection remains the same for the reasons set forth in the previous Office action and for the reasons set forth below.

Chikara teaches a pharmaceutical composition for the prophylactic treatment of migranes comprising an aqueous extract of *Sapindus trifoliatus* pericap (0.1-1 % w/v) (See Abstract), which inherently contains hederagenin (See page 11, lines 10-13) and *Emblica officinalis* (0.1-1 % w/v) in acidic conditions (please note that Chikara further teaches that the pH of the composition is maintained between 3.5 and 7.0, wherein a pH range between 3.5 and 5.5 is most preferred, See page 18, lines 20 and 21), which reads on an extract of the paricarp of the fruit of *Sapindus trifoliatus* comprising hederagenin and at least one pharmaceutically acceptable additive. Chikara further teaches that the pharmaceutical composition further comprises an isotonic agent, such as sodium chloride (See page 19, lines 1 and 2), which reads on a tonicity agent. Chikara further teaches that the composition is obtained in the form of nasal drops (See

Abstract) and that the fruit of *Sapindus trifoliatus* is used in the treatment of epilepsy (See page 11, lines 1-9), which reads on anticonvulsant.

The teachings of Chikara are set forth above. Chikara does not expressly teach an anticonvulsant pharmaceutical composition for nasal administration comprising of an extract of the pericarp of *S. trifoliatus* comprising from 0.001 to 1.0 % w/v hederagenin nor does Chikara teach hederagenin in an amount from 0.004% of 0.08% w/v nor does Chikara teach that the extract is in the form of a lyophilized powder, nor does Chikara teach that the pH is in the range of between 4.5 and 6.5. However, at the time the invention was made, it would have been obvious to one of ordinary skill in the art and one would have been motivated and had a reasonable expectation of success to modify the amount of hederagenin in the composition taught by Chikara, to modify the form in which the extract of pericarp is in and to modify the pH of the composition, because at the time the invention was made, it was known that the paricarp of the fruit of *Sapindus trifoliatus* inherently contained hederagenin, as clearly taught by Chikara. Furthermore, it would have been merely a matter of judicious selection to one of ordinary skill in the art at the time the invention was made to modify the referenced composition because it would have been well in the purview of one of ordinary skill in the art practicing the invention to pick and choose a concentration of hederagenin, it would have been well in the purview of one of ordinary skill in the art to choose a form that an extract was in, particularly since the extract was being made into a composition further comprising a pharmaceutically acceptable additive (please note that lyophilizing the extract simply makes the extract more concentrated since it is simply removing extraction solvent),

and it would have been well in the purview of one of ordinary skill in the art to modify the pH of the composition to provide an anticonvulsant pharmaceutical composition for nasal administration and for prophylactic treatment of migrane comprising hederagenin, because at the time the invention was made, it was known in the art that the paricarp of the fruit of *Sapindus trifoliatus* inherently contained hederagenin and that it was useful for treating migranes and epilepsy, as clearly taught by Chikara. Thus, the claimed invention is no more than the routine optimization of a result effect variable.

The result-effective adjustment of particular conventional working conditions (e.g., modifying the amount of a bioactive compound in a composition, using a desired form of an extract, and adjusting the pH of a solution) is deemed merely a matter of judicious selection and routine optimization which is well within the purview of the skilled artisan.

Furthermore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to add any of the claimed ingredients in the making of the claimed composition because it is well known that its *prima facie* obvious to combine two or more ingredients, each of which is taught by the prior art, to be useful for the same purpose in order to form a third composition which is useful for the same purpose. The idea for combining them flows logically from their having been used individually in the prior art. *In re Susi*, 58 CCPA 1074, 1079-80; 440 F.2d 442, 445; 169 USPQ 423, 426 (1971); *In re Crocketti*, 47 CCPA 1018, 1020-21; 279 F.2d 274, 276-277; 126 USPQ 186, 188 (1960).

Based upon the beneficial teachings of the cited references, the skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Accordingly, the claimed invention was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, especially in the absence of evidence to the contrary.

Applicant's arguments have been fully considered but they are not persuasive.

Applicant argues that the Declaration of Arora demonstrates non-obviousness of the claimed invention over Chikara and that the Office Action does not properly recognize the evidence that Chikara teaches away from the claimed invention and there would have been no reason for one of ordinary skill in the art to deviate from the teaching of Chikara. Applicant further argues that since Applicants have fully enabled the invention they are claiming, the teachings of Chikara are not the only teachings that provide enablement for Applicant's invention; therefore, the Chikara reference does not teach or suggest the invention for which Applicants are enabled.

In response to Applicant's arguments above, to Applicant's argument that the claims of the present application are styled in "consisting essentially of" form and as indicated in MPEP section 2111.03, this term is intended to limit the scope of the claims to the specified materials or steps and those that do not materially affect the basic and novel characteristic(s) of the claimed invention. *See In re Herz,* 537 F.2d 549, *551-552,* 1990 U.S.P.Q. *461,* 463 (C.C.P.A. 1976). In the present case, it is undisputed that the Chikara reference discloses a composition that includes *Sapindus trifoliatus and*

Emblica officinalis, and to Applicant's argument that, as demonstrated by the data submitted herewith in the Declaration of Sudershan K. Arora, the presence of the *Emblica officinalis* in the composition disclosed by Chikara is indeed sufficient to destroy the basic novel characteristics of the claimed invention, the presence of *Emblica officinalis* significantly affects receptor binding properties of a composition that includes *Sapindus trifoliatus*, and Chikara therefore not only fails to disclose the present invention, Chikara teaches directly away from the present invention, this is not found persuasive because Applicants have neglected to show that an aqueous extract of *Sapindus trifolatus* provides the instantly claimed effects, and, therefore, since Applicants are not fully enabled for the invention they are claiming, the teachings of Chikara are the only teachings that provide enablement for Applicants invention. Therefore, the Chikara rejection teaches the invention for which Applicants are enabled.

Response to Amendment

The declaration under 37 CFR 1.132 filed 06/11/2008 is insufficient to overcome the rejection of claims 1-6, 10 and 11 based upon the rejection under 35 U.S.C. 103(a) as being unpatentable over Chikara et al. (N*) as set forth in the last Office action because: Applicant is not fully enabled by Applicant's originally filed specification (please see 112 1st rejection applied above), and, therefore, since Applicant is only enabled for the composition taught by Chikara et al. (N*). Therefore, Applicant's declaration, which essentially recites what was already disclosed in Applicant's

originally filed specification and is not fully enabled, is not sufficient to overcome this rejection.

No claims are allowed.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy L. Clark whose telephone number is (571)272-1310. The examiner can normally be reached on Monday to Friday between 8:30am - 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Terry McKelvey can be reached on (571) 272-0775. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Amy L. Clark
AU 1655

Amy L. Clark
September 12, 2008

/Michele Flood/
Primary Examiner, Art Unit 1655